MEDICAL PROCEEDINGS

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REDAKSIONEEL · EDITORIAL

WEER EENS DIE PRYS VAN GENEESMIDDELS*

Almal wat by die ontdekking, vervaardiging, voorskryf en toebereiding van geneesmiddels betrokke is, is seker al sat daarvan om gedurig op die een of ander aanklag in die beskuldigdebank geplaas te word. 'n Mens sou amper dink dat al die verskillende groepe persone wat vir die terapeutiese oorwinnings van die huidige eeu verantwoordelik was, niks anders as 'n klomp misdadigers is nie. Dié wat by die farmaseutiese bedryf betrokke is sowel as dié wat in aptekerswinkels werk, gaan, net soos hul medemense, onder een groot nadeel gebuk —hulle is menslik, en dit is net so menslik om 'n fout in die bestuur van 'n groot en weldadige bedryf te begaan as wat dit is om jou aan 'n vergissing in 'n nie-skeppende beroep soos die staatsdiens skuldig te maak. Die politici wat ons lotgevalle in die verkeerde baan lei en tog probeer om die Gesondheidsdiens te administreer, kan ewe maklik gelyk as ongelyk hê.

Hierdie soort gedagtes ontstaan ongetwyfeld van tyd tot tyd by dié mense wat dit vir die moderne dokter moontlik maak om sy werk te doen, en vir die moderne pasiënte om te herstel van siektes wat sy vriende en familiebetrekkinge skaars drie dekades gelede doodgemaak het.

Die farmaseutiese bedryf, net soos diegene wat kritiek daarop uitoefen, het gefouteer in etlike rigtings wat vandag maar al te goed be-

* Herdruk, met verlof van die Redakteur van die *British Medical Journal*, uit die uitgawe gedagteken 12 Augustus 1961, bladsy 441.

DRUG COSTS AGAIN*

Everyone concerned with the discovery, manufacture, prescribing, and dispensing of drugs must be getting a little tired of appearing in the dock on this charge or the other. Anyone would think that all the various groups of people responsible for the therapeutic triumphs of the modern era were a bunch of crooks. Those working in the pharmaceutical industry as well as those working in chemists' shops share one great disadvantage with their fellow creatures—they are human. It is as human to err in the conduct of a great and beneficent industry as it is to make mistakes in such an uncreative calling as the Civil Service. The politicians who misguide our destinies and yet try to administer the Health Service are just as likely to be wrong as to be right.

Some such thoughts as these must from time to time be harboured by those people who make it possible for the modern doctor to do his work, and for the modern patient to recover from diseases which killed his friends and relations a bare three decades ago.

The pharmaceutical industry has, like all those who criticize it, erred in a number of directions, all of which are now boringly familiar to the readers of mass-produced magazines. The medical press here and in the U.S.A. has been sharply critical of certain ad-

* Reproduced by permission of the Editor of the *British Medical Journal*, from the issue dated 12 August 1961, p. 441.

kend is aan die lesers van tydskrifte met 'n groot sirkulasie. Die mediese pers hier te lande en in die Verenigde State het kwaai kritiek uitgeoefen op sekere reklamenuwighede wat oënskynlik meer kwaad as goed gedoen het; en die bedryf se eie handelsvereniging is sterk genoeg om 'n demper op die onbesonnenheid van sy minder verantwoordelike lede te plaas. Maar nou verneem ons uit die *Derde Verslag* van die Komitee insake Openbare Rekeninge[1] (lees ook die *Aanhangsel* op bl. 121) dat daar weer eens ondersoek ingestel gaan word na reklamekoste en die ‚aansienlike bedrae wat fabrikante bestee aan verkoopsbevordering, toegespits op algemene praktisyns en hospitaaldokters.'

Met gerusstellende ongekunsteldheid verklaar die komitee voorts:

‚Daar word erken dat dokters beïnvloed word vir sover dit hul voorskrifgewoontes betref deur verteenwoordigers wat glad met die tong is, en deur uitvoerige leesstof, die koste waarvan deur die prys van geneesmiddels weerspieël moet word.'

Hulle gaan die Departement dus aanpor om volledige inligting hieroor aan hulle te verstrek ‚sodat dit moontlik sal wees om te *oordeel* of buitensporige reklamekoste die pryse wat deur die Gesondheidsdiens betaal word, opdryf.' (Ons kursiveer.) 'n Mens voel geneig om te vra: Wie is hulle om te oordeel, en hoe gaan hulle dit doen? Die Minister van Gesondheid kan dit by sy lys van kunsmatige elemente in die Gesondheidsdiens voeg.[2]

Die uitgewers van mediese tydskrifte—insluitende die B.M.A.—sal moontlik daarby baat as advertensies in verband met geneesmiddels net in mediese tydskrifte verskyn. Talle dokters het van tyd tot tyd reeds gekla oor die stortvloed van leesstof wat in hul briewebusse te lande kom. Maar ons wil in alle nederigheid aan die Komitee insake Openbare Rekeninge en aan die Gesondheidsdepartement die wenk gee dat die geneesmiddelbedryf sy eie besigheid waarskynlik beter as enigiemand anders ken, en dat die bedryf dit makliker sal vind om sy groot voordele tot beskikking van die publiek en die mediese professie te stel as sy bekladder ophou om die bedryf as 'n werppyl-skyf in 'n plaaslike kroeg te behandel.

1. *Derde Verslag van die Komitee insake Openbare Rekeninge.* 1960-61-sitting. Londen, H.M.S.O. Prys 2s. netto.
2. *The Elephant and the Whale* (1961): Brit. Med. J., **1**, 1479.

vertising gimmicks that were thought to do harm rather than good; and the industry's own trade association is strong enough to curb the indiscretion of its less responsible members. But now, as we read in the *Third Report* from the Committee of Public Accounts[1] (see *Supplement,* p. 121), once again there is to be a probing into the costs of advertising and the 'considerable expenditure by manufacturers on sales promotion directed to general practitioners and hospital doctors.'

With disarming naïvety the committee goes on to say this:

'It is admitted that doctors are influenced in their prescribing habits by persuasive representatives and elaborate literature, the cost of which must be reflected in the prices of the drugs.'

So they are going to prod the Ministry to give them full information on this 'so that it will be possible to *judge* whether extravagant advertising costs are inflating the prices paid by the Health Service.' (Our italics.) One must ask, who are they to judge, and how? The Minister of Health can add this to his list of artificial elements in the Health Service.[2]

The proprietors of medical journals—including the B.M.A.—would possibly benefit if advertising drugs was confined to medical periodicals. Plenty of doctors have written from time to time to complain about the spate of literature that goes through the letterbox. But we would humbly suggest to the Committee of Public Accounts and the Ministry of Health that the drug trade probably knows its own business best and will find it easier to continue to give its great benefits to the public and to the medical profession if its detractors cease to regard it as a darts board in a local pub.

1. *Third Report from the Committee of Public Accounts.* Session 1960-61. London, H.M.S.O. Price 2s. net.
2. *The Elephant and the Whale* (1961): Brit. Med. J., **1**, 1479.

ABSTRACT

MUMPS ORCHITIS TREATED WITH CORTISONE AND CORTICOTROPHIN

The author surveys current treatment for mumps orchitis and describes 2 cases treated with cortisone and corticotrophin. Local therapy may be helpful, whilst surgical treatment is effective in very acute bilateral testicular involvement. Oestrogens may be used prophylactically in males who have passed the age of puberty. Theoretically, passive immunization with plasma, blood or gamma globulins is advisable, but in practice this can rarely be applied. The antibiotics at present available are ineffective. Modern treatment of this testicular complication utilizes cortisone and corticotrophin.

[van den Bon, P. (1957): Ned. Tijdschr. Geneesk., **101**, 753.]

MEDICAL GERONTOLOGY

PROSPECTS FOR LONGEVITY

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There is at present no consensus as to what senescence really is. The previous articles,[1, 2] discussing the various definitions and some of the effects of senescence, only emphasize the fact that no single factor can be identified as the explanation of the different types of senescence. Various factors contribute in varying proportions to these changes, which include deterioration of essential structures, the additive effect of previous injuries, progressive change in cellular morphology and responses, and change in organ functions.

Many authors feel that senescence must of necessity occur in all men, and that the span of life must be finite. The length of a person's life is also determined by several factors, some of which have been studied and recorded. By the manipulation of these the span of life has been increased.

The possibility of amelioration or removal of the degenerative diseases and infections has been studied and applied extensively. Theoretically the removal of these causes of death should increase the span of life to its maximum. The most significant increase has been in the younger age groups. The increase in the survival rate of the young and the middle-aged, from the turn of the Century, is one of the important causes of the increase in the number of the elderly in the present population.

The chances of survival or the expectation of life of the older age groups, however, has increased only slightly. The average life expectancy of males aged 65 was 11.5 years in 1900-1902, and 12.9 years in 1956. For females the figures were 12.2 and 15.5 respectively.[3] These figures cover the period of the extensive application of the use of the antibiotics as well. The effect of the progress in medical treatment has been, therefore, not so much the increase of life expectancy of the older age groups as the survival of larger numbers of middle-aged to old age. This was forcefully emphasized by Titmuss at the 3rd Congress of the International Association of Gerontology held in London in 1954.[4]

Extension of the span of life in the elderly person by improved medical care does not imply at the present time the complete arrest or the elimination of disease. Many are disabled by these degenerative diseases. Benjamin,[5] expressing similar views, states:

> 'The social and medical services . . . will face a growing burden of chronic invalidity arising from the sheer growth in numbers of older persons outstripping the slower improvement in their average vitality.'

The limits of application of prevention, curative treatment and supportive measures have, however, not yet been reached. The possibility of marked decrease in these diseases still remains.

Longevity has been correlated with many vital characteristics. These include brain weight, body weight, the length of gestation and the rate of metabolism. The significance of these relationships is not yet clear.

Numerous studies have emphasized the genetic basis of longevity. These are reviewed briefly by Close[6] and by Rockstein.[7]

Pearl[8] showed a correlation between longevity of parents and that of their progeny. The work was based on calculations and correlations of the life span of the 2 parents and the 4 grandparents of any individual. Studies of the life span of twins also showed this correlation. The differences in dizygote twins were consistently larger than in the monozygote twins. It was felt by Kollman and Jarvik[9] that these extensive studies demonstrated a genetically determined relationship between parental and progeny life expectancy.

Included in the genetic factors controlling life span is sex. It is well established that the life expectancy of females exceeds that of the male in all groups and ages.

There is no known gene which is responsible for the increase in the life span. A contrary view has, therefore, been expressed. The genetically determined specific diseases shorten the life span, and their absence determines the longevity of some strains. This has been supported by experimental work with mice.[10]

Lansing[11] has demonstrated what is probably a cytoplasmic factor influencing the life span. Experiments with rotifers showed that the age of the mother affects the longevity of the off-

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spring, genetic factors being constant. This factor appears at the time of cessation of growth. Longevity could be sharply reduced by repeatedly selecting eggs from old mothers for propagating each successive generation. This was reversible by altering the procedure and selecting eggs from adolescent mothers. It was these experiments that led Lansing to the conclusion that senescence is a phenomenon which begins at the time of maturity.[12]

The best prospect for prolongation of life lies in that of the slowing down of changes of senescence before they manifest themselves. Nutrition and environmental temperature are factors which influence the rate of senescence, and can be varied.

McCay[13] raised immature rats on a diet containing all the essential nutritional materials but lacking sufficient calories to promote growth and maturation. These rats remained in a state of immaturity and also lived far longer than the litter mates on a normal diet.

Lansing,[10] in his experiments with rotifers, also showed retarded ageing with retarded growth and increased maximal size. When applied to children, Sinclair[14] felt that the slower than average rate of growth achieved by limiting the diet is to be regarded as the normal rate, if it results in an increased life span.

The other aspect of overfeeding as a cause of early ageing with a short life span, has also been well supported by experimental evidence. Sinclair[14] reviews the work done which demonstrates this danger.

The conclusion drawn is that the overfeeding and the present pursuit of quick growth and development of children is not compatible with maximal longevity as adults. Shock[15] and Donahue[16] see in these results support for their viewpoint that ageing commences even before maturity is reached.

In adults, too, it has been well shown that over-nourishment shortens the life span.[17] Weight reduction will correct the defect.

Boulière,[18] in discussing the comparative biology of ageing, reviews the findings of the effects of environmental temperature on senescence. A rise in temperature accelerates the process in insects, fishes, amphibians and reptiles. Although this may be a factor, it is probably limited in warm-blooded animals with closely regulated body temperatures. On the other hand, low temperatures have been used to preserve human tissues. Conservation of both animals and men have been achieved by cooling the whole organism.

Attempts at the reversal of the changes of senescence, when already established, have been made for many centuries. One must mention the Fountain of Youth, the Philosopher's Stone, and the use of blood or various organs of young animals and man. More recently, Niehans has developed the use of fresh tissues and cells of various organs by injection to stimulate and rejuvenate the human organism. Parhan and Aslan advocate the use of 2% Novocaine solution. Special honey destined for future queen bees has been well advertised as having similar properties. There is, however, no sure method of rejuvenation.

Those who have retained their physical and mental abilities to advanced years have not been studied adequately. The increasing number of nonagenarians and centenarians, who take an active part in daily living, provide evidence that senescence is not inevitable. Kaplan[19] says:

'It is reasonable to hope that an extensive study of these fortunate people will teach us how to spread the blessings of physical and mental vigor more widely among the elderly.'

With this hope of an increased span of life ahead, one must mention the purpose of these studies and their application. There is no better way than to quote the viewpoint of Shock.[20]

'The ultimate goal of action programs in the field of aging is to minimize the individual and social handicaps of old age as they now exist. This means giving every individual the maximum opportunity for healthy old age, with meaning to himself and his community."

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CONVERGING ADVANCES IN PSYCHIATRIC GENETICS AND THE PHARMACOLOGY OF PSYCHOTROPIC DRUGS*

RESEARCH IMPLICATIONS

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The borderland between two disciplines is often a fertile field for new insights and discovery in science. The mere fact of bringing to awareness the relatedness of two such areas may be sufficient to disclose vistas of advance that would not come to view from the vantage point of either in isolation. Such, in my submission, is the case with the enzyme block hypothesis as applied to psychiatric genetics when it is brought into juxtaposition with neuropsychopharmacology, including its potent pharmaceuticals, the MAO inhibitors and imipramine. It is accordingly the purpose of this paper to bring together salient findings from psychiatric genetics and neuropsychopharmacology to show how, when considered in interrelationship, these two disciplines are mutually fructifying.

RELEVANT FACTS FROM THE SPHERE OF PSYCHIATRIC GENETICS

It is to the monumental researches of Franz J. Kallmann that we owe our assured scientific knowledge of the specific autosomal hereditary basis of the endogenous psychoses. To summarize his conclusions, the genetic mechanism is single recessive in schizophrenia (adult and pre-adolescent), irregularly single dominant in manic depressive psychosis, while in involutional psychosis we are dealing with heterozygous carriers of the schizophrenic genotype. This latter finding accords well with the rigidity of the prepsychotic personalities of these cases as well as the atypical features of the depression characterizing the developed clinical picture. These facts are presented in compendious form with a list of detailed references in Kallmann's *Heredity in Health and Mental Disorder*.[1]

Eliot Slater's[2] work on the other side of the Atlantic, well documented in his *Psychotic and Neurotic Illnesses in Twins*, is in essential agreement with that of Kallmann. Points at issue between these two authorities, notably the existence of dominant as well as recessive forms of schizophrenia, in no way affects the validity of the enzyme block hypothesis upon which the thesis of the present paper depends.

Table 1 embodies the genetic findings of Kallmann, Slater and some other contributors to this field.

THE CHEMICAL BASIS OF GENE ACTION

CONTROL OF PROTEIN AND ENZYME SYNTHESIS BY DNA

Central to the understanding of protein and enzyme synthesis, and hence the deviations of enzyme synthesis known as enzyme blocks underlying genetic diseases, is the role of the deoxyribonucleic acids (DNA), the nucleic acids chiefly concerned in the control or organization of the process. Brown and Todd[12] have shown DNA molecules to be long, thread-like structures of high molecular weight, com-

*A paper read at the Third World Congress of Psychiatry in Montreal, 4–10 June 1961.

monly known as macromolecules. Chemically they are polynucleotides, differing from one another in the nature and sequence of the nitrogenous bases attached to the chain. Although the story is far from complete, it is supposed that different sections of the DNA macromolecule control the synthesis—or carry the information necessary for the synthesis—of different enzymes. This information is disposed along the macromolecule like words on a tape, and DNA is to the cell what the information tape is to automation. On this analogy a gene may be likened to a phrase or sentence. If nucleic acids control protein manufacture, what is it that controls DNA manufacture? The answer seems to be that these compounds are able to reduplicate themselves in a manner that the Watson-Crick model seeks to illustrate—the two complementary strands separate by unwinding, and each rebuilds its missing partner.

TABLE 1: GENETIC FINDINGS IN THE ENDOGENOUS PSYCHOSES

Psychiatric Condition	*Investigator*	*General Population*	*Half-Sibs*	*Sibs*	*Two-Egg Twins*	*One-Egg Twins*	*Parents*	*Children*	*Genetic Mechanism*
1. Manic-Depressive Psychosis	Kallmann	0·4%	16·7%	23·0%	26·3%	95·7%	23·4%		Autosomal irregular dominant.
	Luxenburger			12·7%	1 : 16	31 : 33		24·4%	
	Rosanoff				11 : 67	16 : 23			
	Stenstedt			c.15%			c.15%	c.15%	
2. Schizophrenia	Kallmann	0·85%	7·1%	14·2%	14·5%	86·2%	9·3%	16·4%	Autosomal recessive: 70% penetrance.
	Slater				14·0%	76·0%			Recessive and dominant cases.
3. Childhood Schizophrenia	Kallmann and Roth			12·2%	17·1%	70·6%	12·5%		Autosomal recessive as in adults
4. Involutional Psychosis	Kallmann	1·0%	4·5%	6·0%	6·0%	60·9%	6·4%		Heterozygous carriers of schizophrenic genotype.

ENZYME BLOCKS

The question of the deflection of metabolic processes through genetically determined enzyme blocks is clearly of central importance in the edifice of the biochemical genetic theory of certain psychiatric states. The details of such blocks are reviewed by Wagner and Mitchell[3] in the field of the inheritance of nutritional requirements of the fungus Neurospora, and Haldane[4] has categorized genetically determined blocks as follows:

1. Failure to produce a catalyst; and
2. Inhibition of metabolic products by

(*a*) another B enzyme being unduly active and producing inhibition of the normal biochemical reaction; or

(*b*) a C enzyme being absent converting B enzyme into something else.

Within the field of psychiatry, phenylketonuria is the paradigm of such genetically determined enzyme blocks. This inborn error of metabolism is inherited as a simple recessive. The biochemical abnormality appears to be an inability to oxidize phenylalanine to tyrosine because of absence or inactivity of the enzyme phenylalaninehydroxidase. It can be formed only in the presence of a single normal gene which these patients lack. It is obviously impossible to supply the missing enzyme. The deficiency of tyrosine can be corrected by giving large quantities of it in the diet but, although this darkens the typical ash-blonde hair and fair skin, it is of no value against the amentia.

An alternative method is to reduce the very high levels of phenylalanine in the blood and urine by feeding a diet which is low in phenylalanine. In 1953 Bickle *et al.*[5] published a report of the successful use of this diet. All the features of the disease, except the amentia, can be reversed in a very short period, but the degree of improvement in the amentia depends on various factors. The children are probably not mentally deficient at birth, but if treatment is long delayed the brain damage is irreversible. There appears to be an upper limit of 2 or 3 years, however, beyond which no further brain damage will take place.

But it is a far cry from the precise chemical detail concerning genetically determined enzyme blocks which we have in respect of phenylketonuria, to our fragmentary information in this respect in the genetically determined endogenous psychoses. It is the purpose of the remainder of this paper to go in search of the enzyme mechanisms concerned by

examining certain general characteristics of enzymes, of physiological and pharmacological substances in the brain and, in conclusion, to pinpoint the issue through a consideration of findings concerning the thymoleptics—the MAO inhibitors and imipramine.

POTENTIALLY SIGNIFICANT GENERAL FEATURES OF ENZYMES

(*a*) *Active Centres and the Formation of Enzyme-Substrate Complexes Thereat.* Although an enzyme may contain many chemically reactive groups, its catalytic activity is confined to a relatively small number of spots on the surface called active centres. Thus trypsin with a molecular weight of 34,000 has only one active centre. Whether enzyme-substrate complexes are formed at the active centres has been found to depend upon the arrangement of atoms both in the enzyme and substrate molecules.

(*b*) *Specificity.* In contrast to inorganic catalysts such as platinum, an enzyme can catalyse only one type of reaction, and sometimes can act only on one particular substance.

(*c*) *Denaturation and Inhibition.* The poisonous nature of metals such as arsenic, mercury and silver is partly explained by enzyme inhibition, related to the fact that the activity of many enzymes depends on the possession of a pair of –SH groups at the active centre or its neighbourhood. Evidence from this field shows how determination of the least number of ions that can cause complete inhibition provides a method of arriving at the number of active centres if the molecular weight of the enzyme is known.

In competitive inhibition we may envisage competition of substance X with the proper substrate S. The 2 compounds formed at the active centre are ES and EX. The extent of the competitive inhibition, in this situation, will depend on the concentration of the inhibitor X. Sulphonamide drugs exert their bacteriostatic effect by the competitive inhibition of enzymes and must accordingly be present in high concentration to be effective.

(*d*) *Co-enzymes.* Certain enzymes which require the presence of a metal in order to function are known as co-enzymes. Thus manganese or magnesium ions are necessary for the hydrolysis of *l*-leucine to amino acid and ammonia. It has been proposed that in such reactions the metal acts as a link between enzyme and substrate.

These 4 principles and limitations of enzyme action may serve as pointers in future research designed to unravel the biochemical details of the aetiology of the endogenous psychoses, implicit in their genetically determined enzymatic nature.

SALIENT ITEMS OF BRAIN CHEMISTRY AND PHARMACOLOGY

Rapid strides have been made in brain chemistry in recent years through the study of such physiological substances as acetylcholine, catechol amines, serotonin and gamma-aminobutyrylcholine (GABA) and their precursors, and such pharmacological substances as the psychotomimetic substances *d*-lysergic acid diethylamide and mescaline and the psychotropic drugs used in therapy such as reserpine, chlorpromazine, the mono-amino oxidase inhibitors and imipramine.

ERGOTROPIC AND TROPHOTROPIC SYSTEMS

A general hypothesis covering much of the data has been ingeniously evolved by Brodie[6] who built on the earlier work of Hess.[7] He postulated that reactions of the organism to changes in the environment are effected by the subcortical system, co-ordinating autonomic, somatic and psychological activity. He suggested that the subcortical system consists of 2 opposing systems which he named *ergotropic* and *trophotropic.*

The *ergotropic system* has the overall effect of preparing the body for positive action. This consists in arousal, increased sympathetic activity, enhanced tone of skeletal muscle and an activated psychological state. The ergotropic division may be an adrenergic system with noradrenaline as its neuro-hormone. It may, anatomically, be the reticular activating system which also is said to be adrenergic.

The *trophotropic system* integrates those conditions which are recuperative in nature. These may be drowsiness and sleep, increased parasympathetic activity, decreased tone in skeletal muscle and lowered responsiveness to external stimuli.

Brodie suggests that the trophotropic system may be regulated by serotonin and that it may be stimulated by reserpine. According to this view, therefore, serotonin and noradrenaline should exert antagonistic effects in the central nervous system and, on this basis, a number of drugs that affect the psyche and behaviour may be placed in 2 categories. The first group

(which includes LSD, mescaline, adrenaline, ephedrine, cocaine and iproniazid) brings about excitement and increased sympathetic activity, sensitivity to external stimuli and skeletal tone. Most of the second group of compounds antagonize the main effects of reserpine and chlorpromazine. On this same basis it should be possible to elicit responses typical of reserpine in 2 ways, i.e. by stimulating the trophotropic system or by depressing the ergotropic system. Chlorpromazine, therefore, might induce a number of central effects similar to those of reserpine, despite the fact that it acts on different mechanisms not involving serotonin. Brodie considers that the difference in the modes of action of these 2 tranquillizing drugs can be explained on the assumption that they act on physiologically antagonistic divisions of the nervous system, reserpine by stimulating the trophotropic system and chlorpromazine by blocking the ergotropic system.

Similarly, a drug should be able to produce signs typical of LSD either by depressing the trophotropic system or by stimulating the ergotropic system. Thus, mescaline and ephedrine might act by stimulating the ergotropic system and LSD itself by depressing the trophotropic system.

There are, of course, many objections to Brodie's theory. It may be that the activity of iproniazid is not related to its ability to block monoamine oxidase. It has been suggested, for example, that iproniazid may act by depleting the tissues of pyridoxine. It is also possible that the reaction of iproniazid with pyridine nucleotides may be of importance. Axelrod[13] maintains that inactivation of monoamine oxidase by iproniazid does not prolong the physiological action of catechol amines in man or other animals, nor does it appreciably alter the excretion of these compounds. He suggests that O-methylation is the principal pathway for metabolism of adrenaline and noradrenaline, whereas monoamine oxidase is mainly concerned in the deamination of the methylated metabolites.

In view of their central importance in the hypothesis just enunciated, as well as in aetiological theory regarding the endogenous psychoses, something more should be said in respect of the catechol amines and serotonin.

THE CATECHOL AMINES

(*a*) The biogenesis of adrenaline is described in the following steps:

Phenylalanine → L-Tyrosine → L-Dopa → Dopamine → Noradrenaline → Adrenaline.

(*b*) The enzymes acting on these biogenic amines are:

Monoamine oxidase (MO) which is inactive towards diamines having 2 amine groups close together and cannot oxidize histamine, and diamine oxidase (DO) which, as its name implies, does act upon diamines but also upon mescaline, which has only one amine group and resembles the phenylethylamines. MO is inhibited by substances including the $=N-NHR$ structure (cyanide, hydrazines, hydrocytamine and semicarbazide), and DO by substances with the $=N-NH_2$ structure (hydrazines). The mode of action of these substances has been variously conceived of as:

i. Inhibition of MO at its site of action, e.g. sympathetic nerve endings;

ii. Involving a primary role of O-methylation in the metabolism of circulating adrenaline; or

iii. Uncertain, inasmuch as a distinction between metabolic degradation and local pharmacological inactivation leaves us with the alternatives of MO and O-methyl transferase within the central nervous system as responsible for the inactivation of catechol amines at their site of action.

SEROTONIN

Serotonin originates in the body as a product of tryptophane metabolism through the steps:
Tryptophane → Hydroxytryptophane (5-HTP) → 5-Hydroxytryptamine (5-HT) or Serotonin.

The reaction requires the presence of pyridoxal-5-phosphate and will therefore be inhibited in a vitamin B_6 deficiency.

The distribution of serotonin is as follows:

Gastro-intestinal tract (mucosa), liver, blood platelets (and spleen, probably derived from blood platelet breakdown) and in lesser concentration in the central nervous system, where it is found chiefly in parts containing central autonomic representation—the hypothalamus, portions of the midbrain and the floor of the fourth ventricle. The finding in the dog brain that the levels of 5-HT and 5-HTP decarboxylase run parallel seems to indicate that 5-HT (serotonin) is synthesized in the central nervous system.

The administration of 5-HTP has been shown to increase the amounts of serotonin in most tissues, including the brain. The amino acid penetrates into cells and is decarboxylated to serotonin wherever the decarboxylase is present. When that level rises to 2 or 3 times that of normal, experimental animals exhibit somatic, autonomic and behavioural effects resembling those produced by LSD. Thus excitement with loss of reflexes, blindness and disorientation, apparent fear and sham rage are among the effects reported. That the action of 5-HTP is due to the serotonin generated is shown by the delay in action, the potentiation

by MAO inhibitors and the relationship of the effects to brain serotonin levels.

The fact that serotonin can be released from the gastro-intestinal tract, platelets and the brain by reserpine has given impetus to the study of storage and release mechanisms. The storage of serotonin in cells in high concentration, protected from monoamine oxidase, suggests that some complex is formed with constituents of the cell which is broken down through the action of reserpine.

Metabolic studies show that serotonin is rapidly oxidized by amine oxidase, first to the aldehyde and then to 5-hydroxy indole acetic acid (5-HIAA). This may, however, be but one of the metabolic pathways, for after injection of 5-HT only a third can be accounted for by an increased amount of 5-HIAA in the urine and only traces of 5-HT are found there. Other studies have shown that up to 25% of 5-HT may be excreted as O-gluconate, and an O-sulphate and an N-acetyl derivative have also been detected in the urine—all possible indicators of alternative metabolic pathways.

The important question of the relationship of serotonin to the aetiology of mental disorder, has been answered affirmatively but in opposite directions by, on the one hand, Woolley and Shaw[8] and, on the other, Orzechowski.[9] The first-named workers suggested that drugs antagonistic to serotonin might act by producing a deficiency of cerebral serotonin and that naturally occurring psychotic states might well result from serotonin deficiency in the brain, attributable to the failure of the normal metabolic processes of synthesis and destruction. Orzechowski, on the other hand, favours the hypothesis of mental disorders arising from an excess rather than a deficiency of serotonin. He argues from the observation that ergot alkaloids cause inhibition of the enzyme amine oxidase, that if amine oxidase were inhibited by the serotonin anti-metabolites, serotonin would accumulate, in which case competition with serotonin would be for the destructive functional site, i.e. the amine oxidase, rather than for the site of action in the brain, resulting in serotonin excess.

There is much evidence to support the hypothesis that serotonin is an important substrate of amine oxidase. This we cannot enter into here. One important finding is that the high concentration of amine oxidase in the liver helps to prevent a flooding of the general circulation with free serotonin.

An assessment of the role of serotonin stems from the original observation by Brodie that reserpine causes a depletion of serotonin from its storage sites in the brain as well as in the platelets and the gastro-intestinal tract. In summary, our knowledge in this field to date is that reserpine itself is short-lived in the brain, but its pharmacological effects persist long after it has disappeared. Brain serotonin is especially sensitive to reserpine: the decline in brain levels occurs within 10 minutes, is 80% complete within 30 minutes, and restitution does not begin for about 36 hours.

THE ISSUE CRYSTALLIZED BY THE SELECTIVE AND COMPARATIVE ACTIONS OF THE MAO INHIBITORS AND IMIPRAMINE

The coming of the anti-depressant drugs, the MAO inhibitors and imipramine have, in their selective actions on the depressions in contrast to schizophrenia, on the one hand, and by their achievement of a similar end result by different chemical pathways in the depressions, on the other, introduced a guiding principle which runs like a golden thread through the complexities of biochemical detail.

SELECTIVITY OF ACTION

In the first place let us consider the implications of the selectivity of the action of these anti-depressant drugs on the depressions *vis-à-vis* schizophrenia in the setting of the genetic background provided by the work of Kallmann, Slater and others. The specific but different single gene mechanisms behind manic-depressive psychosis and schizophrenia might be conceived as entering into the aetiology of these conditions in one of two possible ways. First, the genetic basis might be regarded as responsible for the constitutions, mental (cyclothymic, schizothymic) and physical (pyknic or endomorphic and asthenic or ectomorphic) underlying the corresponding psychoses. Secondly, the 2 genes concerned may be conceived as supplying 2 different chemical elicitors or exaggerators of the 2 underlying temperaments (cyclothymic and schizothymic) —these 2 chemical elicitors resulting from the derailed metabolism brought about by the genetically determined enzyme blocks involved.

Our own work[10] with the psychotomimetic drugs LSD and mescaline, in line with world experience in this field, favours by analogy the second type of hypothesis for the naturally occurring endogenous psychoses, inasmuch as schizophrenic and manic-depressive components present in vestigial form in the normal personalities concerned are apparently elicited.

The matter is taken a step further by the selective action of the anti-depressant drugs (MAO inhibitors and imipramine), endorsed by South African[11] and world experience, which quite emphatically supports the second hypothesis of 2 different genetically determined chemical elicitors in the 2 psychoses, one only of which is inhibited by the anti-depressant drugs.

SIMILAR END RESULT BY ALTERNATIVE CHEMICAL ROUTES

We turn now to the second point, the achievement of a similar end result by alternative chemical routes, as exemplified by the action of the MAO inhibitors (Niamid, Nardil, Parnate and Marplan) on the one hand, and imipramine (Tofranil) on the other. For the implications of this let us compare the modes of action of the 2 groups of substances.

Sufficient has already been said about the mode of action of the MAO inhibitors and their effect on serotonin and the catechol amines.

The main central actions of imipramine, conveyed to me in a personal communication by Drs. Exer and Ziegler of Basle, are as follows. It is not an MAO inhibitor although it does have a blocking effect on the catechol amines. It raises the serotonin level in the brain without doing so in the platelets, posing the question whether this implicates the blood-brain barrier or whether the difference can be explained by differential direct action on brain and platelets. Rat experiments show diminution in certain enzyme concentrations as with chlorpromazine: specifically there is a decrease in the formation of the co-enzyme (Dopa) of transaminases and decarboxylases, but there is no effect on the adrenaline level in the brain. In common with psychotropic drugs in general, imipramine has an anti-oxidant action on the brain as tested on brain slices *in vitro*, which finds a parallel in pathological brain studies revealing that imipramine reduces the amount of lipofuchsin (oxidation product of fats and fatty acids) accumulating in the brains of elderly patients.

In the liver a high dosage of imipramine results in uncoupling of ATP and oxidative phosphorylation.

With regard to peripheral effects, imipramine has the action of cholinesterase inhibition at the ganglion. Sympathetic effects are are claimed to be connected with the inhibition more marked than parasympathetic ones, and of catechol amines. But lest we lose sight of the wood for the trees, let us consider a very small Table comparing the effects of reserpine, MAO inhibitors and imipramine on serotonin level in the brain and blood platelets (Table 2).

The common feature that strikes one immediately is that shared by the 2 groups of drugs with the similar (anti-depressant) clinical effect, viz. raised brain serotonin level. This not only confirms Woolley and Shaw's insight into the central importance of serotonin in the aetiology of the psychoses, or at least one of them (manic-depressive psychosis), but also upholds their view (in this psychosis), in opposition to Orzechowski, that the trouble is a deficiency, not an excess, of serotonin.

TABLE 2

	Brain	*Platelets*
Reserpine	—	—
MAO Inhibitors ..	+	+
Imipramine	+	—

The trophotropic component of Brodie's system having received such spectacular support from a comparison of the actions of anti-depressant drugs, what may be said of the ergotropic component, or the adrenergic system? Here, too, experience with imipramine, it will have been noticed, shows significant similarities to those of the MAO inhibitors—in such findings as blocking of catechol amines, decrease in dopamine formation, and the predominant peripheral sympathetic action.

CONCLUSIONS

By and large the comparison of the mechanisms whereby the 2 groups of anti-depressants achieve their results has yielded these 2 important conclusions:

1. The fact that the 2 types of anti-depressants (MAO inhibitors and imipramine), despite fundamental differences in chemical structure and numerous differences in their detailed chemical effects, nevertheless exercise a similar influence on serotonin and the catechol amines, strengthens the view that these are the significant chemical entities involved in the therapeutic action of both types of drug.

2. In so doing it pinpoints our search for the aetiological enzyme block postulated by genetic evidence to the field of serotonin and the catechol amines and their progenors.

Prospects. It is thus in the depressive phase of manic depressive psychosis that the most detailed biochemical links with basic considerations in genetic aetiology have been forged. It is interesting to speculate whether a new drug which claims a potent therapeutic action in mania, Haloperidol, a substituted butyrophenone, will through detailed biochemical and pharmacological study afford insights comparable to those disclosed for the depressive phase by the anti-depressant drugs. Equally specific leads for the exploration of the situation in schizophrenia are not yet to hand, although high-dosage insulin therapy (which presumably breaks into the deranged state of metabolic events at a somewhat peripheral point) and the palliative effect of high-dosage tranquillizers may hold out some clues.

In our further researches into the nature of the enzyme blocks involved in each of the endogenous psychoses, in addition to the special leads we have already examined, the potentially significant general features of enzymes reviewed at an earlier stage of this paper provide general indications for our guidance. Thus the paucity of active centres and also the specificity of enzyme action holds out the hope that our search is a limited, not an infinite one. The formation of enzyme complexes at the active centres is illumined by the principle that there is an interdependence of the arrangement of atoms in the enzyme and substrate molecules. Denaturation and inhibition of enzymes by metallic poisons suggest a possible parallel to the biochemical noxae postulated in the pathogenesis of schizophrenia. It will be remembered in this connexion that such inhibition was related to the fact that the activity of many enzymes depends on the possession of a pair of –SH groups at the active centre or in the neighbourhood. The process of competitive inhibition may be relevant as it provides some analogy to the antimetabolite concept so important in Woolley's work on serotonin; and finally, a possible role of trace elements, such as manganese and magnesium, underlying co-enzyme action, which have been shown to have therapeutic action in diabetes mellitus, may well form part of our present quest as well.

SUMMARY

Two converging trends in modern psychiatric research and practice are reviewed in this paper, as it is the author's conviction that a clearer appreciation of the interrelationships between them will have a cross-fertilizing effect on both disciplines, to the enrichment of our aetiological conceptions and applications in the therapeutic field alike.

First, the evidence adduced by psychiatric geneticists, notably Franz J. Kallmann in America and Eliot Slater in Britain, that specific and separate genetic predispositions underlie schizophrenia and manic-depressive psychosis, receives consideration. The inference stemming from modern genetic theory, that in general the nature of this aetiological gene action is biochemical, and in particular related to enzyme blocks, is then developed.

Secondly, salient features of the vast new fields of enzyme chemistry, neurochemistry and neuropsychopharmacology, including psychotomimetic and psychotropic drugs are passed under review.

In conclusion, the 2 broad converging trends of psychiatric genetics and neuropsychopharmacology are brought to a more defined focus by considering the implications of the specificity of action for the depressive states *vis-à-vis* schizophrenia of the anti-depressant drugs, and of the similarity of clinical outcome in the field of the depressions of drugs with different chemical modes of action as illustrated by the potent modern medicaments, the MAO inhibitors and imipramine.

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MEDICO-LEGAL SECTION

DEATH DUE TO CHLOROFORM*

REX, *Respondent* v. BLOM, *Appellant.*

(Bloemfontein—Cape Town)

1938. *October* 27, 28; *November* 10. STRATFORD, C.J., DE WET, J.A., WATERMEYER, J.A., TINDALL, J.A., and CENTLIVRES, A.J.A.

On a charge of murder there was evidence justifying the conclusion that the deceased had been murdered and her dead body placed on a railway line where it had been mutilated by a passing train. The effect of the medical evidence was that death was due to a sudden shock which might have been caused by a blow on the head or by chloroform applied in concentrated form on the face. The doctors could not say which alternative was the true cause inasmuch as the deceased's head had been crushed by the passing train and, if death was due to chloroform, no trace of it would be expected after the time that had elapsed between the death and the post-mortem examination. The Crown proved that the accused had a motive for killing the deceased and the opportunity to do so; that on the day of the murder the accused had purchased chloroform; giving a false name and a false explanation for the purchase; that after the murder he had given inconsistent explanations to a doctor as to the cause of a strain from which he was suffering; and that upon his arrest he had denied ever having had a chloroform bottle in his possession. The accused's defence was an alibi, but he gave no evidence himself and the trial Court drew the inference, in the absence of any explanation by the accused, that the deceased had died as the result of the administration of chloroform by the accused. Upon a question of law reserved as to whether there was evidence upon which a reasonable man could convict.

Held, that, having regard to all the circumstances of the case, including the conduct of the accused and his failure to give any explanation of such conduct, there was evidence upon which a reasonable man could come to the conclusion that death was due to the administration of chloroform and that such chloroform had been administered by the accused.

STRATFORD, C.J., The accused was convicted by PITTMAN, J., sitting with two magistrates as assessors, of the murder on the 29th April, 1938, of a native woman aged between 20 and 30 years. At the conclusion of the trial three questions of law were reserved for the decision of this Court and a special entry was made which was based on an alleged irregularity.

The first question reserved being whether there was evidence on which a reasonable man could convict, it is necessary to mention the main facts and the findings of the trial Court.

The evidence as to the findings of the body and what was observed at the place where it was found and at the *post mortem* examination held about 15 hours after death is thus summarised in the judgment of PITTMAN, J.:—

"At a few minutes past 10 on the night of Friday, April 29th last, a passenger train, travelling from Rosmead to Graaff-Reinet, ran over the body of a native woman, Elsie Yalola. This body was lying across the left-hand rail at a spot some fifteen miles from Graaff-Reinet and 220 yards on the Rosmead side of the cottage, No. 48, of a railway ganger, Marais. There since the commencement of the month the woman had been in domestic service. After being struck by the engine the body was dragged about 10 feet and then thrown off the line to the left. It had been observed from the engine by the stoker, Koekemoer, when the distance between him and it was between 20 and 30 yards, but he realised that it was a human body only when this distance had been reduced to some 10 or 12 yards. Koekemoer observed no movement whatever in the body before the impact. Its close proximity at the moment it was observed by him is explained by a bend in the line which prevented the headlights of the engine playing upon the particular spot where the body lay on the line, until such moment. Immediately Koekemoer observed the object he shouted to the driver, van der Merwe, to stop the train, but, though van der Merwe acted at once upon this direction he was unable to avoid an impact. The train was brought to a standstilll

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only after the engine at least had reached a spot on the line on the Graaff-Reinet side of the ganger's cottage. As it approached the body the engine's whistle had been blown, and the rumbling noise made by the train itself was intensified by the nature of the gradient, downward, and by the surrounding hills. The ganger, Marais, was summoned and immediate investigations were set on foot. These revealed the mutilated condition of the body, the woman's body, over which the train had passed. This was left untouched throughout the night, and the next morning between 8 and 9, in the position in which it had been thrown by the train, it was examined by Dr. van Schalkwyk, the district surgeon, and Dr. Naude. The former some four hours later conducted his official *post mortem.* Each of these doctors gave it as his opinion, Dr. Naude rather more strongly than Dr. van Schalkwyk, that the woman was already dead at the time the train passed over her body. This conclusion they rested upon the meagre quantity of blood which had come from injuries clearly attributable to the impact. There was an arm severed above the elbow, a toe and portion of a foot cut off, and on incised wound about 4 inches long and 1 inch deep on the inner side of the left thigh. From none of these injuries, so caused, had blood been exuded in a manner and to an extent consistent with infliction before death even upon an anæsthetised body. It is true that from the skull, apparently crushed in the impact, a considerable amount of blood appeared to have issued on to the ground after the body had been thrown to the side of the line, but this issue, the doctors said, was consistent with *post mortem* injury. The head is the seat of a large quantity of blood, and the situation of the corpse at the spot was such as would cause this blood to find its way on to the ground beneath the head. The corpse when the doctors saw it had been lying in that situation for some 10 to 11 hours.

"The opinion held by the doctors that death occurred before the train struck the body raises the enquiry how death was caused. The body, in their view dead, lay across the rail. With the possible exception of the head there was then no external portion of it bearing indication of any previously-inflicted mortal injury. The throat, for instance, had not been cut, nor had any other fatal found been inflicted. Nor was there any sign that the woman had been strangled. All existence upon the body of indications which would have evidenced any such injury was directly negatived. Leaving aside the head, all the injuries which *post mortem* observations disclosed were presumably caused as the result of the train's impact, and—to judge from the absence of bleeding—after death. Only upon the head does it appear possible that there may have been injuries inflicted before the train ran over the body. There may have been a blow with some heavy instrument, a stab with a knife, or some other head injury, all indication of which was destroyed in the extensive damage to the skull undoubtedly caused by the train. But had there been any such blow or stab to cause death, then the wound would almost certainly have bled, and blood would have been found at the spot where the head was resting, as the body lay on the line, before the train ran over it. Also a doek which the woman had been wearing, found between the rails immediately after the impact and apparently struck from her head as the train swept along, would presumably have been bloodstained or borne other indications of the injury. But there were none such on the doek. Their absence and the absence of blood where the body was first lying render strong support to the conclusion that, assuming the woman was dead as her body lay across the rail, she met her death as the result of some other instrumentality than violence causing external lesion.

"On the indications such instrumentality may well have been the administration of chloroform or some substance of similar properties in the manner suggested by the Crown. There was no trace internally of any poison, and nothing there to account for sudden death. The woman was last seen alive just before nine, apparently perfectly healthy. Her death, which occurred not more than at most about an hour later, could have been caused by inhalation of chloroform, notwithstanding that all traces of such inhalation had disappeared by the time the railway witnesses came upon the body."

The effect of the medical evidence accepted by the trial Court is that death was due to sudden shock. Such shock causing death might be caused by a blow on the head or by chloroform applied in concentrated form to the face; but the doctors could not say whether the shock in the present case was due to a blow on the head or to chloroform; for the head had been crushed by the train after death, and if death were caused by the application of chloroform to the face no trace of it would be expected after the time that elapsed between the death and the *post mortem* examination in this case.

The main features of the evidence against the accused, which was circumstantial, are mentioned in the judgment, which also gives findings on certain evidence led by the Crown for the purpose of proving that the accused had a motive for killing the native woman Elsie. At the time of her death Elsie, who had previously had two children by a coloured man, had been pregnant for five or six months. The trial Court found, on certain evidence led by the Crown, that sexual intimacy had existed between the accused and the deceased for some months before her death, that in March and April he was trying to find the means of securing an abortion, that he gave Elsie mixtures containing certain ingredients, that the conclusion was irresistible that he was responsible for her pregnancy, and that therefore there was no absence of motive to weaken the evidence connecting him with the crime.

The main features of this evidence were the following: On the afternoon of 29th April the accused bought an ounce of pure chloroform from a chemist in Graaff-Reinet, signing the false name of Swart in the poison register and stating falsely that a teacher on the farm Willow Slope, where his parents lived, wanted the chloroform to make a poison bottle for insects. On 18th May, the day of accused's arrest, when Inspector Talken showed him a search warrant and told him he was looking for a chloroform bottle, the accused remarked that he had never had such a thing in his possession.

It appears that in April the deceased was employed by the witness Marais, a ganger, whose cottage was about 220 yards from the spot on the line where the body was found. This spot is about 21 miles north-east of Graaff-Reinet and "Willow Slope" is 4 miles further in the same direction. The accused was seen at about 5.30 p.m. on 29th April travelling on a bicycle at a spot about 13 miles outside Graaff-Reinet and 8 miles from the spot where the body was found. These distances are taken in a direct line, and the actual distances by road may have been somewhat greater. He was travelling at the time on a road leading past the ganger's cottage and on to "Willow Slope." The accused, who gave no evidence himself, called his brother, the latter's wife and certain other witnesses to prove that on the evening and the night in question the accused was on his brother's farm "Die Draai," two miles east of Graaff-Reinet, and that therefore he could not have been travelling on his bicycle 13 miles to the north-east of Graaff-Reinet at 5.30 p.m. and could not have been at the spot where Elsie met with her death between 9 and 10 p.m. The trial Court did not believe the witnesses called by the defence in support of this *alibi*. Mention must also be made of certain statements made by the accused after the death of the deceased. On 29th March, a month before the death of Elsie, the accused consulted Dr. Naude about an injury which he ascribed to a fall. The doctor strapped the side of his chest and prescribed for the pain he felt there. After a fortnight his condition was so much improved that further treatment was unnecessary. The doctor expressed the opinion in evidence that the accused would have had very little difficulty in riding a bicycle except immediately after the accident. On 1st May, two days after Elsie was killed, the accused again consulted Dr. Naude, complaining of a recurrence of pain in the side of the chest, and the doctor applied strapping again. On this occasion the accused told Dr. Naude that the pain had been caused by a journey on a motor bicycle to Aberdeen. About a week later, when receiving further treatment from Dr. Naude, he volunteered the statement that the recurrence of the pain had been caused by lifting a sack of quinces. When Dr. Naude reminded him of his previous explanation he denied having said that the cause was a journey on a motor bicycle. On this occasion he also told Dr. Naude that he "must stand by him as he was suspected in connection with the murder of the native girl who had been run over by the train." The remark of PITTMAN, J., that the accused's statements to Dr. Naude are not without significance is justified in the absence of any explanation by the accused. The fresh explanation and the denial of the former one may have been due to his realising that the truth of the alleged journey to Aberdeen could be tested by the police, whereas the verification of the other would be a difficult matter. Those conflicting statements to Dr. Naude, though by themselves they could not justify any definite inference, are a relevant part of the circumstantial evidence, bearing in mind that the lifting or pulling of Elsie's body on to the railway line would have involved considerable muscular effort on the part of the culprit.

The remarks of PITTMAN, J., in giving the verdict of the Court concluded with the following sentences: "The defence evidence setting up an *alibi* on behalf of the accused we find wholly unacceptable. He himself remained out of the witness box. We have endeavoured to attach no more than its due weight to his failure to give evidence, but we feel bound

to confess that when so much has been brought out calling for an explanation his omission directly to give one has very strongly militated against him. We conclude by saying that a motive urging him to do away with this woman worked strongly on his mind, that he had the fullest opportunity to indulge this motive, anad that he possessed himself secretly of the necessary means. The circumstances under which the woman met her death satisfy us that it was the accused, situated as he was, who caused it.

The above is a summary of the material evidence in the case and of the Court's findings upon it: we have now to consider the argument so ably presented by Mr. *Snitcher* for the accused.

At the outset let me state that in our view there was undoubtedly evidence justifying a reasonable conclusion that this woman met her death by violence at the hands of another, that is to say she was murdered, and also there was evidence justifying the finding that death was not caused by the impact with the engine of the train—she was dead when her body was placed across the line. The inference that the murderer was the person who so placed the corpse after having perpetrated the crime is one that cannot reasonably be challenged. So much we must regard as the hypothesis of the problem. Now the indictment is framed in general terms, viz., that the accused "did wrongfully . . . . and maliciously kill and murder Elsie Yalola"; no particulars were requested or given. But from the evidence for the Crown laid before the Court and from the verdict there can be no question that the prosecution set itself the task of proving that the deceased met her death as a result of the administration of chloroform by the accused, and the case must be considered on exactly the same footing as it should be if that cause of death had been expressly particularised in the indictment. And it is in this connection that the argument of Mr. *Snitcher* gets its most plausible force. It is said that when the Crown avowedly sets out to prove that the accused committed the crime in a particular manner, the cause of death, so alleged, must be proved without reasonable doubt. Moreover, on the facts of the present case, unless the Court was justifiably satisfied that the deceased's death was the result of an application of chloroform, the verdict cannot stand. So far I am in agreement with counsel for the accused. In the nature of the case death must have been caused by chloroform or the accused must go free. So much must be conceded, for if any other agency was the cause of death the evidence against the accused is only that he had a motive for the commission of the crime and (on the finding) an opportunity to commit it. Such evidence alone would not, I think, justify conviction in the circumstances of the present case. The Crown did not contend the contrary, nor do I gather from the reasoning of the presiding Judge that the trial Court rested its verdict on such limited evidence. Indeed, by mutual agreement the question before us must be answered one way or the other by the existence or absence of evidence justifying the conclusion that an administration of chloroform killed the deceased Elsie Yalola. The question of law reserved is thus reducible to the following: Was there any evidence from which a reasonable man might properly conclude that the deceased was killed by the administration of chloroform? And it is in this connection that it is said that the Crown completely failed since from evidence of motive and opportunity the cause of death could not be inferred, and without the inference or proof of the latter the accused—so the argument ran—could not be connected with the crime. Put in another form the argument, on the facts of the case, is that, once it is conceded (as it is conceded) that the Crown must prove this particular cause of death such proof is a prerequisite to any verdict against the accused. Thus far, I think, the argument of counsel is sound, for I agree that the verdict can only be supported if the trial Court was satisfied beyond reasonable doubt that chloroform was the instrument of death employed and also if there was legal evidence justifying such conclusion. From the actual verdict and from the remarks of the learned Judge quoted above it is proper to conclude that the trial Court entertained no doubt that chloroform was the cause of death. It is, however, the existence of evidence to support that finding which is strenuously challenged. This is the crux of the case, and the difference between the rival contentions which we have to consider can be very shortly stated. For the accused it is said there was no evidence whatever on this all-important issue, that all that was elicited from the two doctors was an opinion that possibly an administration of chloroform caused the death of the deceased. Now, if in considering the evidence on this issue, we must exclude reference to the conduct and words of the accused both before and after the murder, it must be admitted that there was no evidence justifying the conclusion as to the cause of death. But

it is in excluding that evidence that the fallacy lies. We were asked, in effect, to consider the evidence in two compartments, that is to say, that before adverting to the evidence relating to the accused's purchase of chloroform under a false name and his false statements and to his statements to Dr. Naude, the Crown had first to prove that chloroform was the cause of death. I understood that it was argued that to refer to the inculpatory words and conduct of the accused as evidence of the cause of death amounted to the logical fallacy of *petitio principii* because, it was said, such conduct and words were only inculpatory on the presupposition that the cause of death by chloroform had been *aliunde* proved. It is here that I do not agree. Limiting the enquiry exclusively to the cause of death, as I do for the moment, the words and conduct of the accused were relevant evidence not only on the accused's connection with the murder but also on the question as to how that murder was committed. It was this twofold bearing of the inference to be drawn from the accused's actions and false statements which has to be borne in mind, and it was the logical inference to be drawn from them, namely that the accused killed the deceased with chloroform which the accused, at the close of the case for the Crown, had to meet.

Though in the above remarks I may be attributing to counsel a line of argument he did not adopt quite in that form, it is none the less necessary, I think, to examine the problem in the way I have done. I now turn to another way of regarding the argument for the accused. It may be said that looking at all the evidence in the case (as I have decided we must), that the Crown did not exclude the probability of death by a blow on the head which did not cause external lesion and, with that probability existing at the close of the case for the prosecution, no inference adverse to the accused could legitimately be drawn from the fact that he did not go into the witness box to explain his conduct and words. This is only another way of saying that, at that stage, there was no *prima facie* case made out that the accused killed the deceased by administering chloroform. To this the reply must necessarily be short and dogmatic. As a matter of logic I cannot agree that no reasonable man could hold that the inference that the accused killed the deceased by the use of chloroform was a more probable one than that she was killed in any other manner. And if that greater probability is conceded, the fact that the accused did not attempt to weaken it by his own testimony was properly taken into the account against him by the trial Court. I have, of course, had regard to the actual evidence given in this case as well as to the words used by PITTMAN, J., in his reasons, but I should add a few remarks about both. As to the first, the probability of death being caused by a blow on the head causing external lesion was rejected because of the absence of blood on the doek. This cause, of course, was excluded without regard to the conduct and false statements of the accused. But the probability of death resulting from a blow (with or without external lesion) is, I think, excluded by the reasoning adopted above. And as to the second, I find the following passage in the judgment: "On the indications such instrumentality may well have been the administration of chloroform or some substance of similar properties in the manner suggested by the Crown." The words "or some substance of similar properties" are not, of course, consistent with the finding that chloroform was the cause, and, as I have said, the latter cause must be found proved to render the accused guilty on the evidence in the case. It must, however, be remembered that the remarks were the Judge's own and should not be regarded as if they constituted a direction to the jury. Having regard to the final conclusion quoted above, it would not be right to attach importance to these somewhat irrelevant words so as to vitiate the final conclusion clearly expressed. That conclusion was that the deceased met her death at the hands of the accused and that the cause of death was chloroform and no other.

The first question reserved must therefore be answered in favour of the Crown.

The next question reserved is the following: "Whether the Court's finding that it was unable to discover the existence of extenuating circumstances was not invalid on the ground that no reasonable man could make such a finding?"

The effect of sec. 338, Act 31 of 1917, as amended by sec. 61 of the General Law Amendment Act, 1935, is that if the trial Court is of opinion that there are extenuating circumstances it may impose any sentence other than the death sentence. It will be observed that even if in the opinion of the trial Court there are certain extenuating circumstances, that Court has still a discretion. That discretion was exercised, and no reasonable ground has been advanced why this Court should interfere with its exercise. The question

reserved must also be answered in favour of the Crown.

The last question of law reserved is: "Whether the admission of the evidence given by the witness Elsa Marais as to the two conversations between her and the deceased woman on the subject of the latter's meeting with one Marthinus was not invalid and prejudiced the accused?"

Assuming that the evidence in question is inadmissible, I find, in relation to it, the following passage in the judgment: "The girl's answers to the two questions mentioned we regard as showing only this, namely, that the deceased may have formed the habit of staving off unwelcome enquiries from Elsa Marais by means of a stock reply. We do not regard them as affording in themselves any evidence that on the night in question the deceased woman, when about to leave the cottage, intended to meet the accused." In view of this statement it is clear that the Court did not regard the hearsay evidence of what the deceased said as affording proof that the deceased left her master's house with the intention of meeting the accused. Thus there was no improper use made of the evidence and in any event no prejudice to the accused. The question is answered in favour of the Crown.

I pass now to the special entry which is based on the ground that the two assessors were in possession of a copy of the record of the preparatory examination. Inasmuch as both assessors in the present case were magistrates, the decision in *Rex* v. *Africaner* (1932, A.D. 86) disposes of the present question. But as under sec. 216 of the Criminal Code, as amended by the General Law Amendment Act, laymen as well as magistrates can be called on as assessors, we should state our view that we see no good reason why assessors should have before them copies of the evidence given at the preparatory examination; indeed we consider that there are serious objections to their reading the evidence before the trial if they are laymen.

Finally there is an application for leave to call fresh evidence. We have before us the general nature of the evidence now sought to be led, and it relates entirely to issues upon which the accused himself could have given the most pertinent evidence. Having regard to the fact that he refrained from giving his own testimony, this is not a case in which this unusual application should be granted.

The conclusion is that the question of law reserved are answered in favour of the Crown, and the appeal based upon the special entry is dismissed and the above application refused.

WATERMEYER, J.A.: Although I have come to the conclusion that the question of law raised in this case should be answered in favour of the Crown, yet since this conclusion has only been arrived at after some doubt I think I should state the reasons which have weighed with me.

The evidence placed before the Court in this case by the Crown was entirely circumstantial and can be arranged under three heads: —

(1) Evidence of the conduct of the accused before the event, showing that he had (*a*) a motive to kill the deceased, (*b*) a design to kill someone.

(2) Evidence to show that accused had an opportunity to kill the deceased.

(3) Evidence of the conduct of the accused after the event showing a guilty conscience.

Under the first head, a motive which might have led the accused to kill the native girl was established by proof that he had had illicit sexual relations with her, that she was pregnant and that he had tried to assist her to procure an abortion. His design to kill someone is arrived at by inference from the fact that he bought chloroform under an assumed name on the afternoon before the girl was killed and that he gave a false reason for its purchase. The inference is that he intended to use the chloroform for an unlawful purpose of such gravity that he thought it necessary to conceal his name and deceive the seller as to his purpose.

Under the third head evidence of a guilty conscience was given by Dr. Naude who said that the accused consulted him two days after the girl was killed with regard to the recurrence of an injury in the nature of a strain in his right side. This strain had been caused originally a month earlier by his falling down a cliff, and he explained the recurrence by saying that he had ridden a motor bicycle to Aberdeen. About a week later he again consulted the doctor with regard to the strain and then he told the doctor that its recurrence had been caused by lifting a sack of quinces, and he denied to the doctor that he had previously told him that it was caused by a ride on a motor cycle to Aberdeen. The inference sought to be drawn from this is that he had injured himself in carrying the body of the dead girl and was afraid that the story of a ride on a motor cycle might be proved to be false. There was also evidence that on 18th May, nearly three weeks after the death of the girl, Inspector Talken showed him a search warrant and

said that he was looking for a chloroform bottle, and the accused then told the Inspector a falsehood by saying that he never had a chloroform bottle in his possession. He was therefore trying to hide from the police the fact that he had had chloroform in his possession some three weeks before, and the inference can be drawn that he had used it for some unlawful purpose.

The accused did not go into the witness box to deny or explain any of the occurrences from which inferences are sought to be drawn, but the effect of that failure to explain must not be misunderstood. His failure to testify merely strengthens the inferences drawn against him, but it in no way strengthens the reasoning based upon those inferences. In other words, the inferences of motive, criminal intention and guilty conscience are strengthened by his failure to testify; but the logical force of further inferences from those inferences (e.g. the inference that because he had a motive to kill the deceased therefore he probably did kill her), is not strengthened by his failure to give evidence. To regard the force of these secondary inferences as strengthened comes very near to putting upon the accused the burden of exonerating himself.

Now it seems clear that if the girl died from the administration of chloroform there is ample evidence upon which the accused could be convicted, but if she died in any other way, then I doubt whether there was sufficient evidence upon which a reasonable man could convict the accused of causing her death. The cause of death, therefore, appears to be the paramount issue in this case, and it is important to note that the determination of the cause of death is entirely a matter of inference from a number of circumstances.

In reasoning by inference there are two cardinal rules of logic which cannot be ignored:

(1) The inference sought to be drawn must be consistent with all the proved facts. If it is not, the inference cannot be drawn.

(2) The proved facts should be such that they exclude every reasonable inference from them save the one sought to be drawn. If they do not exclude other reasonable inferences, then there must be a doubt whether the inference sought to be drawn is correct.

I now come to consider the question whether it can be inferred from the evidence in the case that the deceased girl died from the administration of chloroform. It appears that the girl's body was mangled by the train, but there was evidence upon which a Court was justified in finding that the girl was dead before the train ran over her. I cannot say that the evidence was clear. The conclusion was an inference drawn by two medical witnesses from the trifling nature of the blood marks found on the spot where the train ran over the body. The inference is a technical one; that is one which cannot be drawn without expert knowledge. But judging by the evidence of the district surgeon the inference could not have been one upon which he felt any great certainty, otherwise he could never have given the following evidence, which I quote from the record:—

"If the person had been alive at the time that the train ran over her, would you have expected to find bleeding or not?

'Not necessarily; it is probable.

"(By the Court): You would probably have found more blood?

"Yes.

"But possibly you might not have done?—Yes.

"Did you come to any conclusion with regard to the body as to whether it had been dead or alive when the train went over it?

"The fact that we saw no blood about the wound in the thigh and the arm made one suspicious that the woman might have been dead before the train struck her.

"(By the Court): That suspicion crossed your mind at the time?

"Yes, we noticed that there was no blood.

"As far as your particular examination of this unfortunate woman is concerned, you are not prepared to express a definite opinion that the girl was dead before the train ran over her?

"No.

"You say there is a suspicion that it might be so?

"Yes.

". . . . It might have been the train running over her causing her death, is that so?—Yes.

"Or it might have been some sudden heart failure on her own part, which you were unable to trace?—It might be.

"And it might be also that she had received a severe blow on the head that you could not see on account of the scattered state of the skull?—Yes.

"You are unable to state the cause of death?

"Yes.

"You are not prepared to say from what you observed that death was due to some criminal action on the part of any person?

"No trace, only a suspicion about the absence of bleeding."

On the whole, however, the medical evidence was such that the Court could come to the conclusion that the girl was dead before the train ran over her, but the cause of her death is still left in doubt by the medical evidence, and this is the point of difficulty in the case. Clearly if the girl died from a blow on the head or in some manner other than by the administration of chloroform, then the accused is entitled to be acquitted because there exists quite a reasonable hypothesis other than murder by the accused (viz. murder by someone else) which would explain her death. The hypothesis is not unreasonable because the girl might have had other lovers (she had had two illegitimate children), she lived alongside a public road, and the evidence showed that she met and talked to a man that night about an hour before her body was found on the line. It becomes necessary therefore to exclude this hypothesis before a conviction could logically follow, and the question before us really resolves itself into this, whether there was evidence before the Court from which an inference could be drawn which would have the effect of excluding this alternative hypothesis.

I have hesitated for a considerable time as to the proper answer to be given to that question. One matter which at first caused me difficulty relates to the probative value of such evidence as the record may furnish because it seems to me that something more than evidence making guilt probable is necessary. Evidence upon which a reasonable man can be satisfied beyond reasonable doubt is required. I am aware that the phrase "proof beyond reasonable doubt" is difficult, if not impossible, to define because of the lack of a standard by which to measure a degree of conviction, but its constant use in criminal cases, as distinguished from the preponderance of probabilities required for proof in a civil case indicates a legal recognition that there are degrees of positiveness or certainty which may exist in the mind of the tribunal called upon to decide a question, and unless Courts are to render mere lip-service to the notion of "proof beyond reasonable doubt" they must give some effect to it. But if the record be considered as a whole I think there was such evidence. If the case be considered without regard to the evidence of Dr. Naude and Inspector Talken, then it would, in my opinion, have been insufficient. It would have related entirely to facts and circumstances antecedent to and coincident with the girl's death, and even if the accused's motive and unlawful design connected with chloroform and opportunity were given their fullest weight, an inference that he killed the girl would not have been justified because in no way could they be regarded as excluding the hypothesis of murder by someone else.

But the evidence of a guilty conscience after the event supplies additional material for inference which when considered together with the other evidence makes it reasonably possible to infer that the accused killed the girl, and that of course leads to a possible further inference that he did it by means of chloroform, and excludes the hypothesis of murder by some other person.

My further difficulty arose from the fact that the Court does not seem to have arrived at its verdict by reasoning along those lines. If the judgment of PITTMAN, J., sets out correctly the reasoning of the Court it is as follows:—

"Only upon the head does it appear possible that there may have been injuries inflicted before the train ran over the body. There may have been a blow with some heavy instrument, a stab with a knife or some other head injury, all indication of which was destroyed in the extensive damage to the skull undoubtedly caused by the train. But had there been any such stab or blow to cause death, then the wound would almost certainly have bled, and blood would have been found at the spot where the head was resting, as the body lay on the line, before the train ran over it. Also a doek which the woman had been wearing, found between the rails immediately after the impact, and apparently struck from her head as the train swept along, would presumably have been bloodstained or borne other indications of the injury. But there were none such on the doek. Their absence and the absence of blood where the body was first lying render strong support to the conclusion that, assuming the woman was dead as her body lay across the rail, she met her death as the result of some other instrumentality than violence causing external lesion. On the indications such instrumentality may well have been the administration of chloroform or some substance of similar properties in the manner suggested by the Crown. There was no trace internally of any poison, and nothing there to account for sudden death. The woman was last seen alive just before nine, apparently perfectly healthy. Her death, which occurred not more than at most about an hour later, could have been caused by inhalation of chloroform, notwithstanding that all traces of such inhalation had disappeared by the time the railway witnesses came upon the body."

I cannot agree with that reasoning. It contains an unjustifiable assumption which forms the basis of inferences, viz., that a blow on the head would most certainly have bled. That assumption leads to the dismissal from consideration of a blow on the head which might have caused death without bleeding.

The result is that a perfectly feasible hypothesis is ignored instead of being excluded, as it should have been, in order reasonably to arrive at the verdict of guilty. But although the reasoning to which I have referred causes difficulty, the verdict is not specifically based upon that reasoning *only*. Mention is also made of the other evidence to which I have referred, and it must have been in the minds of the members of the Court when they reached their conclusion. Such being the case, it is impossible to say that they would not have arrived at exactly the same verdict even if they had realised the oversight contained in the passage I have quoted.

In the circumstances the question before us, whether there was evidence before the Court upon which a reasonable man could convict must be answered in favour of the Crown. On the other questions raised I agree with the judgment of the CHIEF-JUSTICE.

TINDALL, J.A.: I agree that the attack on the verdict in this case cannot succeed. I commence by saying that there was undoubtedly evidence on which a reasonable man might properly find that the deceased was dead before her body was placed on the railway line; for the medical evidence in favour of that finding, based on the absence of blood on the line, was accepted by the trial Court. Moreover there was evidence on which a reasonable man might properly find that her death was due to violence. When she left her master's premises, about an hour before her body was found, she was apparently in good health, the *post mortem* examination revealed no symptoms of disease which might account for a sudden death from natural cause. It cannot be said that the trial Court acted unreasonably in excluding self-inflicted violence and accident as possible causes. Indeed, if she was dead before her body was mutilated by the engine, the inference that she was killed by violence and that the person who killed her put her body on the line is based on very strong grounds. Accordingly this Court is bound to consider the first question of law reserved on the hypothesis that the deceased was killed by violence and that the culprit placed her body on the line to prevent discovery of the real cause of death.

The strongest argument on behalf of the accused was that there was no evidence at all that the cause of death was chloroform and therefore the fact that he was in possession of chloroform did not connect him with the crime and that the Crown case based on circumstantial evidence did not call for any answering testimony on the part of the accused.

Now it is true that the Crown was unable to prove the cause of death by direct evidence or by evidence based on the *post mortem* examination. The effect of the medical evidence accepted by the trial Court is that death was due to sudden shock. Sudden shock causing death might be caused by a blow on the head or by chloroform applied in concentrated form to the face but the doctors could not say whether the shock in the present case was due to a blow on the head or to chloroform; for the head had been crushed by the train after death and where death is caused by the application of chloroform to the face no trace of it would be expected after the time that elapsed between death and examination in this case. In view of the medical evidence it is not likely that PITTMAN J., overlooked the possibility that death was caused by a blow on the head which caused no external lesion; he must have considered that possibility but on the circumstantial evidence he came to the conclusion that the cause of death was chloroform applied to the face.

I cannot agree that in charges of homicide it is essential to prove the cause of death by direct evidence or medical evidence based on *post mortem* examination. No doubt the Crown is expected to prove the cause of death by such evidence where it is available. But where, owing to the manner in which the body of the victim has been dealt with, such evidence cannot be adduced, the Crown may conceivably be able to discharge the *onus* of proving the cause of death by other evidence.

Wills on *Circumstantial Evidence* (7th ed., p. 357), in dealing with the three prepositions which must be made out to establish the *corpus delicti* in cases of homicide (namely that death has taken place, that the body is identified with the person alleged to have been killed and that death was due to unlawful violence or criminal negligence), states that in the great majority of cases the moral conduct of the person accused or suspected has little or nothing to do with the investigation of death, identity or foul play; but the author adds that it would be going too far to say that moral conduct of an accused or suspected person can have no bearing on any of these questions.

I can see no reason why evidence of the acts of an accused person should not under certain circumstances be held to establish the cause of death beyond a reasonable doubt. One may mention, as an illustration, the case where the evidence shows that an accused obtained possession of an unusual means of causing death, that he told a witness that his object in obtaining such means was to kill a certain person and that subsequent acts of his indicated that he had carried out his object.

In the present case there was evidence on which the trial Court might properly find that the accused obtained the chloroform for an evil purpose. The false reason mentioned by him for its purchase, the signing of a false name in the chemist's poison register, the denial to Inspector Talken that he ever possessed a bottle of chloroform are facts which, in the absence of any explanation by the accused of his purchase of a lethal agency rarely in the possession of persons other than doctors and chemists, support such an inference.

Then, was there evidence on which a reasonable man might properly find that such evil purpose was the killing of the deceased? The main facts relied on by the Crown were the purchase of the chloroform the same afternoon, the presence of the accused on his bicycle at 5.30 p.m. at a spot on the road about eight miles from the place where the body was found which suggested a journey in that direction, his attempt to disprove the possibility of his presence at that spot by the evidence of the witnesses who stated that he was then at his brother's farm "Die Draai," his conversation with Dr. Naude on 1st May when he accounted for the recurrence of a pain in the side of his chest by stating that he had ridden a motor bicycle to Aberdeen, his statement a week later to the same witness that the recurrence of the pain was due to lifting a weight (a bag of quinces), his denial, when the doctor reminded him of his previous explanation, that he had given such explanation and his statement to Dr. Naude a week or more before his arrest on 18th May that he was suspected in connection with the murder of the native girl who had been run over by the train and that the doctor must stand by him; his failure to go into the witness box and explain any of the said circumstances. All these circumstances, coupled with the strong motive on the part of the accused to get the deceased out of the way and thus prevent the exposure of his illicit relations with her, at least make it highly probable that he bought the chloroform with the object of administering it to the deceased and that he did administer it to her and thus caused her death.

Can we say that, in the absence of direct evidence that the deceased was killed by chloroform, the purchase of chloroform under the circumstances was no evidence against the accused and that no reasonable man could hold, as the trial Court did, that the failure of the accused to give evidence was a factor telling against him? I do not think this Court would be justified in so holding. It has been argued that in attaching significance to the purchase of the chloroform the trial Court reasoned in a circle by first assuming that death was caused by chloroform. I cannot agree that such an illogicality underlies the reasoning of the trial Court. That reasoning seems to have been that the circumstantial evidence as a whole, in the absence of explanation by the accused, led to the inference that he bought the chloroform to apply it to Elsie, that he did so and thus killed her and thereafter put her body on the railway line. The Court was aware that it could not convict if it felt a reasonable doubt. Difficulty has always been found in attempting to define what is meant by proof without a reasonable doubt. The degree of proof that a reasonable Court will require to convince it of guilt will vary to some extent with the individual judge or juryman. Stephen (*General View of the Criminal Law,* p. 184), in a passage quoted by the present CHIEF JUSTICE in *Rex* v. *Kumalo* (1930, A.D. 214), states, with reference to the commonly expressed saying that the prisoner is entitled to the benefit of every reasonable doubt, that "it may be stated otherwise, but not, I think, more definitely, by saying that before a man is convicted of a crime, every supposition not in itself improbable which is consistent with his innocence ought to be negatived." In the present case the trial Court evidently took the view that *prima facie* the circumstantial evidence already mentioned was such that it could find no reasonable hypothesis on which to reconcile it with the innocence of the accused, and that as the accused had not offered any explanation which would support an innocent interpretation of his acts, all the circumstances convinced the Court that death was not due to a blow on the head but to the application of chloroform. There is nothing to show that the trial Court misdirected itself or that its reasoning was faulty. I am not prepared to say that on a reasonable view of all the evidence the trial Court could not properly be convinced of the accused's guilt.

I agree that the main question of law reserved must be answered in favour of the

Crown. I do not think it necessary to deal with the other questions raised except to say that I agree that all of them must fail.

CENTLIVRES, A.J.A.: I agree that there was evidence upon which a reasonable man could convict the accused of the crime of murder. It seems to me that it was incumbent on the Crown to prove beyond a reasonable doubt that (1) a death had taken place, (2) the deceased was identified with the person alleged to have been killed, (3) the death was due to an unnatural cause other than accident or suicide, (4) the accused was the person who killed the deceased. There is no dispute in this case that the Crown proved (1) and (2). As to (3) there was ample evidence to justify the inference that death was due to an unnatural cause other than accident or suicide. Under (3) I do not think that it is necessary in all cases for the Crown to prove the specific cause of death, but usually the Crown sets out to do this in order to connect the accused with the death. When it succeeds in proving the specific cause of death and in proving that the accused not only had in his possession the means to bring about that specific cause of death as well as the opportunity then a reasonable man may draw the inference from these facts and other circumstances which are proved that it was the accused that killed the deceased. As to (4) there was—as is usually the case in crimes of this nature—only circumstantial evidence to connect the accused with the killing of the deceased. That circumstantial evidence consisted of the acts and movements of the accused prior to the death of the deceased and the conduct of the accused after that event. It seems to me that circumstantial evidence of this nature may be used to draw two inferences—(*a*) as to the specific cause of the death, provided that that cause has not been ruled out by other evidence whether medical or otherwise, and (*b*) as to the person who caused the death. See Wills on *Circumstantial Evidence* (7th ed., p. 389) who says: "In most criminal charges, the evidence of the *corpus delicti* is separable from that which applies to the indication of the offender, but in cases of poisoning it is often impossible to obtain conclusive evidence of the *corpus delicti,* irrespectively of the explanatory evidence of moral conduct."

On page 385 the learned author, after pointing out that some vegetable poisons are beyond the reach of chemical processes, and, under certain conditions, also beyond the reach of physiological methods comes to the conclusion that "it would be most unreasonable and lead to the grossest injustice, and in some circumstances impunity for the worst of crimes, to require, as an imperative rule of law, that the fact of poisoning shall be established by any special and exclusive medium of proof, when that kind of proof is unobtainable, and specially if it has been rendered so by the act of the offender himself."

In the case of death caused by the application of chloroform to the face there would—according to the medical evidence adduced in this case—be no trace of it left after the time that elapsed between the death and the *post mortem* examination. This is, therefore, one of those cases where it was impossible for the Crown, without the assistance of evidence as to the acts and conduct of the accused before and after the death, to prove the specific cause of the death. Moreover, a reasonable man can, in my opinion, draw the inference from the evidence adduced in this case that the person who killed the deceased placed her dead body on the railway line. This act of the culprit rendered it impossible for the Crown to eliminate, without the assistance of the evidence referred to above, every violent cause of death other than the administration of chloroform.

It is not necessary, in view of the judgments prepared by my brethren, to refer to the details of the circumstantial evidence. It is sufficient for me to say that, in my opinion, it is impossible for this Court to say that there was no evidence on which a reasonable man could find that the accused killed the deceased by applying chloroform to her face. When the judgment of the trial Court is read as a whole this is, I think, the finding at which it arrives. In cases such as *Rex* v. *Cilliers* (1937, A.D. at pp. 288 and 289), "the conviction was expressly made to rest upon the evidence mentioned in the judgment and upon the reasoning therein adopted. To cases such as that the remarks quoted from the judgment have full application. In my judgment, however, they cannot properly be applied to the present case" (*per* STRATFORD, C.J., in *Rex* v. *Gordon,* 1938, A.D. at p. 255). The latter case shows that small errors in the process of reasoning cannot, in the circumstances relating to the summing up (such circumstances being present both in that case and in this case), properly be relied upon to vitiate a verdict otherwise justified on the evidence.

I agree with the order proposed to be made by the CHIEF JUSTICE.

DE WET, J.A., concurred.

Appeal accordingly dismissed.

NOTES AND NEWS : BERIGTE

Dr. S. C. Appleton, of Cape Town, has left for a visit to London and the Continent.

He will spend a week with Professor Francois in Ghent and attend the Jules Gonin Club Conference in Lausanne before returning on 15 October.

* * *

Dr. J. H. S. Gear, Director of the South African Institute for Medical Research, recently returned from Geneva where he spent 4 weeks at the World Health Organization attending meetings of Scientific Study Groups on Bilharziasis, Virus Diseases and Trachoma, serving as Chairman of the first two and Rapporteur of the third meeting. He represented the Institute at the 43rd Medical Congress of the M.A.S.A. and presented a paper on *Virus Diseases in Infancy.*

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ELI LILLY MEDICAL RESEARCH FELLOWSHIP (SOUTH AFRICA): 1961

Dr. Louis A. du Plessis of Johannesburg has been appointed to this Award for 1961.

Dr. Louis A. du Plessis

Dr. du Plessis' research programme will be devoted to the prosthetic replacement of the human mitral valve. He will work at the National Heart Institute, Bethesda, Maryland, U.S.A.

* * *

BOOTS MEDICAL APPOINTMENT DIARY FOR 1962

A very limited supply of this useful Diary has been received for distribution to medical practitioners in South Africa. Import restrictions have made it impossible to obtain quantities to meet all demands.

Medical practitioners are therefore urged to request their copies of this Diary as soon as possible from:

B.P.D. (South Africa) (Pty.) Limited,
P.O. Box 45,
Jeppestown, Transvaal.

COUNCIL FOR SCIENTIFIC AND INDUSTRIAL RESEARCH

UNITED STATES PUBLIC HEALTH SERVICE INTERNATIONAL POSTDOCTORAL RESEARCH FELLOWSHIPS

INFORMATION STATEMENT

The development of research in medicine and biology has been strengthened in the United States by periods of study and research spent by citizens of this country in the laboratories of other countries. For many years the National Institutes of Health of the Public Health Service has helped to finance this productive interchange. It has now become possible to extend the U.S. Public Health Service fellowship programme through the award of a limited number of fellowships to highly qualified scientists from outside the United States to work in the medical and biological laboratories of this country.

The research training of these scientists from other countries will be financed to strengthen medical research throughout the world. It will give these outstanding scientists in health-related fields a chance to share knowledge with kindred groups by conducting research in the United States. The fellows, as well as the host laboratories, should benefit from this exchange of knowledge and techniques.

The National Institutes of Health intend to administer this programme so as to make the work of the scientists from abroad most productive. Experience has shown that an essential part of this process is a clear understanding of the terms and conditions under which the fellowships are awarded. These terms and conditions, which have been developed with the advice of scientists from the other countries, are outlined below.

One particularly important condition of the awards, noted below in Part IV, is that the fellows return to their home countries.

I. *Method of Applying.* Appropriate national research organizations have been authorized to nominate fellows. These organizations may obtain application forms, together with necessary instructions and information, from the National Institutes of Health. The secretary of a national research organization should send to the National Institutes of Health only completed applications which the organization has formally endorsed as meeting the conditions set down in the following section.

II. *Minimum Requirements.* The candidate must have:

(*a*) Obtained a doctoral degree or its equivalent in one of the medical or related sciences and also have demonstrated outstanding research promise.

(*b*) Made satisfactory arrangements with a laboratory in the United States at which he proposes to train. (Such arrangements are often made through correspondence between a senior scientist and a counterpart in the United States where a suitable research opportunity or training in the applicant's field of interest can be provided. Copies of such correspondence should accompany the application.) A Facilities and Commitment Statement blank for this purpose will be forwarded in each application packet.

(*c*) Acquired a workable reading and speaking knowledge of the English language.

(*d*) Demonstrated proficiency in research, with indication that he will pursue a research and/or

academic career for a reasonable period after training.

(*e*) Met such standards as are required by his own national research organization.

III. *Period and Terms of Award.*

(*a*) *Period of Award.* Awards will usually be made for one year, but a second year or part thereof may be approved when adequately justified. Application for extension must be made through the committee which made the original nomination. Nominations for extension will constitute one of the allowable nominations from that country and not an additional one. Final approval will be by the committee at the National Institutes of Health.

(*b*) *Stipend and Allowances.*

1. A stipend of $4,500 is provided. In addition, $500 is provided for spouse and each dependent child, whether or not the dependants accompany the fellow to the United States.

2. Travel for the fellow only (not for dependants) is provided at the rate of 8 cents per mile from home to laboratory in the United States and return.

3. No allowance will be made for shipment of personal or household effects.

(*c*) Beginning Dates. The fellow may commence training at any date which he and his laboratory of choice find convenient, within ten months of formal notification of award.

(*d*) *Report of Activities.* A brief written report of scientific activities shall be prepared by the fellow at the end of his visit, to permit evaluation of scientific utility of the foreign fellowship program.

IV. *Passports and Visas.* Fellows will be responsible for obtaining passports and visas required for entrance into the United States. All fellowship awards are made subject to ability of the applicant to obtain the necessary papers for entry into the United States. A letter of appointment and a letter authorizing the use of the exchange-visitor number for obtaining an exchange-visitor's visa are provided by the National Institutes of Health to successful applicants. This type of visa requires that the fellow return to his homeland after completion of training.

V. *Visit to the National Institutes of Health.* All fellows will be welcome to visit the National Institutes of Health for a brief period. The Foreign Grants and Awards office should be notified of intent to visit at least one month in advance.

VI. *General Information.*

(*a*) *Payment of Stipends.* Pay begins upon the fellow's arrival in the United States. The sponsoring institution will have been given a grant from which the fellow will receive funds to cover his stipend, dependency allowances, travel, and laboratory expenses.

If emergency funds are required early in the fellowship tenure, the sponsoring laboratory or institution may make such funds available, and this advance will be deducted gradually from subsequent stipends.

(*b*) *Laboratory Expenses.* An amount of $500 for each year of the fellowship will be provided as a part of the grant to the institution. These funds may be used for any purpose which the institution concludes will further the fellow's research training, including transportation costs and *per diem* allowance to permit attendance at a scientific meeting within the United States.

(*c*) *Income Taxes.* Stipends and dependency allowances up to $300 per month paid for this programme will normally not be declarable as income under the U.S. Federal Income Tax Law, although an individual tax return must be filed annually. Fellows are urged to consult university officials on this matter shortly after arrival.

(*d*) *Health and Accident Insurance.* Health and accident insurance will be required of all fellows through a group policy maintained by certain United States Government agencies for non-citizens who are in the United States for training. The premium for such insurance is set annually. The current insurance rates will be quoted at the time of award. The premium will be advanced from grant funds but the grant will be reimbursed through deductions from pay checks to the fellow.

(*e*) *Special Information and Assistance.* If any difficulties arise after arrival in the United States, or if further information is required, the fellow may communicate with the Chief, Foreign Grants and Awards, Division of General Medical Sciences, National Institutes of Health, Bethesda 14, Maryland (telephone OLivet 6-4000, Extension 4335, or WHitehall 6-3231). The fellow will be assisted in any way possible.

The CSIR has been nominated as the official body responsible in South Africa for these awards and application forms may be obtained from the Administrative Officer-in-Charge, Medical Research/Research Grants Division, CSIR, P.O. Box 395, Pretoria.

The closing date for applications is the 10 October 1961.

Applicants will be given until the 15 December 1961, to submit the Facilities and Commitment Statement called for in paragraph II (*b*).

PREPARATIONS AND APPLIANCES

FERROCEBRIN

(IRON, VITAMIN B COMPOUND, AND VITAMIN C. LILLY)

Composition: Each 5c.c. (about one teaspoonful) contains:

Ferrous Sulphate (equivalent to 20 mg. of iron)	100 mg.
Thiamine Hydrochloride (Vitamin B_1)	1 mg.
Riboflavin (Vitamin B_2)	1 mg.
Pyridoxine Hydrochloride (Vitamin B_6)	0.5 mg.
Vitamin B_{12} Crystalline	5 mcg.
Pantothenic Acid (as d-Panthenol)	1 mg.
Nicotinamide	5 mg.
Ascorbic Acid (Vitamin C)	35 mg.

Alcohol, 2%.

Uses: For the prevention and treatment of iron-deficiency anaemia and the prevention of vitamin B complex and vitamin C deficiencies. **Ferrocebrin** plays a practical role in helping to restore vitality to the child who is underweight, easily fatigued, or anorexic because of mild anaemia. It is also indicated for elderly anaemic patients who prefer liquid medication.

Dosage: A bright-yellow liquid with a wild strawberry flavour, **Ferrocebrin** is readily accepted, whether administered by spoon or mixed with formula, water or fruit juice.

Infants and Children: 1/2—1 teaspoonful (preferably at mealtime) 3 times daily.

Adults: 1—2 teaspoonfuls (preferably at mealtime) 3times daily.

Supply: Liquid No. 34, in 118-c.c. bottles.